Chronic cough as a neuropathic disorder

Kian Fan Chung, Lorcan McGarvey, Stuart B Mazzone

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Experimental Studies Unit, National Heart & Lung Institute, Imperial College London, London, UK (Prof K F Chung DSc); **Biomedical Research Unit, Royal Brompton Hospital, London, UK** (K F Chung); **Centre for Infection and Immunity, The Queen's University of Belfast, Belfast, UK** (L McGarvey MD); **and Laboratory of Respiratory Neuroscience and Mucosal Immunity, School of Biomedical Sciences, The University of Queensland, St Lucia, QLD, Australia** (S B Mazzone PhD)

Correspondence to: Prof K F Chung, National Heart & Lung Institute, Imperial College London, Dovehouse St, London SW3 6LY, UK **f.chung@imperial.ac.uk**

Chronic cough is a common symptom that can be a daunting challenge for clinicians since treatment of the underlying cause does not always provide adequate relief, an obvious cause can remain elusive, and current antitussives have fairly poor efficacy and undesirable side-effects. Patients with chronic cough typically describe a range of sensory symptoms suggestive of upper-airway and laryngeal neural dysfunction. Additionally, patients often report cough triggered by low-level physical and chemical stimuli, which is suggestive of cough-reflex hyperresponsiveness. Pathophysiological mechanisms underlying peripheral and central augmentation of the afferent cough pathways have been identified, and compelling evidence exists for a neuropathy of vagal sensory nerves after upper-respiratory viral infections or exposure to allergic and non-allergic irritants. In this Personal View, we argue that chronic cough is a neuropathic disorder that arises from neural damage caused by a range of inflammatory, infective, and allergic factors. In support of this idea, we discuss evidence of successful treatment of chronic cough with agents used for treatment of neuropathic pain, such as gabapentin and amitriptyline. Regarding cough as a neuropathic disorder could lead to new, more effective antitussives.

Introduction

Cough is a common symptom in patients with a range of respiratory and non-respiratory diseases, and it has been subdivided into acute and chronic cough dependent on duration. An acute cough that lasts for less than 3 weeks is self-limiting and typically secondary to an upper-respiratory-tract infection, whereas a cough that persists for more than 8 weeks is termed chronic, and often the symptom has persisted for much longer than 8 weeks by the time of presentation. Whereas acute, self-limiting cough remains a disorder for which supportive measures are adequate, chronic cough, which can persist for months and years, is a difficult clinical problem largely because of poor understanding of the pathophysiological processes involved and the absence of effective antitussive therapies. Results of some epidemiologic studies[1–4] suggest that chronic cough is very prevalent in the community (9–33%) and could be increasing in association with rising environmental pollution. Many patients seek medical advice because a chronic cough can seriously impair quality of life.[5] Although a cause for the cough can be apparent in most patients, in a substantial proportion (ranging from 7% to 40%) no underlying cause can be identified and the cough is referred to as idiopathic or unexplained.[1] Irrespective of whether or not the cause can be identified, the most consistent pathophysiological finding in patients with chronic cough is an abnormal upregulation of the cough reflex, manifest by heightened tussive responses to citric acid or capsaicin inhalation (figure 1).[6,7] This idea of cough hypersensitivity is gaining broader recognition among physicians, but so far little explanation for this important clinical notion has been suggested. In this Personal View, we argue that cough hypersensitivity arises from a neuropathic disorder that affects the cough afferent pathways.

Chronic cough as a neuropathic process

A persistent or intermittent tickling, irritating sensation, rawness in the pharynx or laryngeal area (sometimes referred to as a feeling of an itch), a choking sensation in the throat, or, less often, a sensation in the chest, can be reported by patients with chronic cough. These sensations result in an urge to cough and often precede the uncontrollable paroxysms of coughing that are typical of chronic cough. Other symptoms include repeated throat clearing, chest tightness, hoarse voice and dysphonia, vocal-cord dysfunction, a globus sensation, and dysphagia;[8] some patients have an irritable larynx.[9] Triggers of cough include changes in ambient temperature, taking a deep breath, laughing, talking on the phone for more than a few minutes, cigarette smoke, aerosol sprays, perfumes, and eating crumbly dry food. These abnormal sensations and triggering of cough by low-level stimuli suggest a disorder of airway sensory neural function, which has led to the introduction of the term chronic cough hypersensitivity syndrome.[8,9] We propose that this disordered sensory neural function (and hence the cough hypersensitivity that underlies chronic cough in general) is caused by an underlying sensory neuropathy.

Support for the notion of neuropathic cough comes from the hereditary, autosomal dominant sensory neuropathy that can be associated with cough, gastro-oesophageal reflux disease, and distal sensory loss.[10,11] Hypersensitivity caused by denervation of the upper airways (laryngeal sensory neuropathy) and oesophagus combined with gastro-oesophageal reflux disease could underlie the cough mechanism. Acidification during repeated reflux events might also cause injury to oesophageal and vagal nerves that regulate airway function, and might therefore contribute to cough in patients with gastro-oesophageal reflux disease.[12,13] Vitamin B_{12} deficiency, which causes a sensory neuropathy, has been suggested as a cause for unexplained cough. Patients with cough and vitamin B_{12} deficiency showed evidence of neuropathy and cough hyperresponsiveness, which resolved with vitamin B_{12} replacement therapy.[14] Neurosarcoidosis and neurofibromatosis localised to the vagus nerves have been reported to cause chronic cough, which provides further evidence for the tussive effect of

sensory neuropathy.[15,16] By contrast, diabetic patients with autonomic neuropathy have diminished cough-reflex sensitivity compared with diabetic patients who do not have autonomic neuropathy and healthy controls.[17]

Afferent cough pathways: peripheral to central

Coughing is both a reflex that requires minimum conscious control and a voluntary behaviour either with or without an accompanying sensory awareness of the need to cough.[18–23] Activation of peripheral sensory nerves is usually the initiating factor that drives the resultant cough, but the outcome can be either reflexive cough with minimum conscious involvement or behavioural cough secondary to the perception of an urge to cough. Reflex cough, behavioural cough, and the urge to cough are three separate entities, each dependent on their own fairly complex neural processes.[23–27] Only vagally-derived sensory neurons can evoke coughing when activated.[28–30] These sensory neurons can be divided into two types: those that have chemosensitive nociceptors, which are characterised by their responsiveness to TRPV1-channel agonists (such as capsaicin from chillies), and those that have low-threshold mechanosensors, characterised by their responsiveness to touch-like mechanical stimuli.[28,31,32] Nociceptive and mechanosensitive vagal afferents provide input to the brainstem at the solitary nucleus and the spinal trigeminal nucleus, with both pathways terminating at distinct and overlapping regions.[33–36] Second-order neurons from the solitary nucleus and the trigeminal nucleus do one of two things; either they project to neurons of the brainstem and spinal respiratory circuit to reflexively modify breathing,[37–39] or they ascend the neuraxis to provide input to several sensory, motor, and cognitive higher-brain nuclei (figure 2).[33] These ascending pathways represent the anatomical basis for sensory perception of airway irritation and provide regulatory control for descending excitatory and inhibitory (behavioural) motor pathways, which terminate both in the brainstem and in the spinal respiratory motor circuits.[23,26,33,40]

Various acute airway stimuli are known to evoke coughing by induction of action potentials in the peripheral axons of the primary sensory neurons in the airways. However, activation of sensory neurons alone is not sufficient to evoke coughing. Rather, specific encoding of the afferent input to the brainstem is necessary, at least to initiate reflex coughing.[24,35] Thus, the central cough-pattern generator depends on fairly high-frequency afferent input for the basic breathing network to be reflexively reorganised into that of a cough motor pattern. Although the mechanisms are not fully understood, high-frequency afferent firing is thought to recruit N-methyl-D-aspartate (NMDA) receptors on second-order neurons in the brainstem.[35] During low-frequency neuronal activity, NMDA receptors are unable to contribute to signalling because of the presence of magnesium ions that block the channel pore. Prolonged depolarisation evoked by high-frequency firing reduces the magnesium block, which greatly potentiates subsequent central network responses to afferent input.

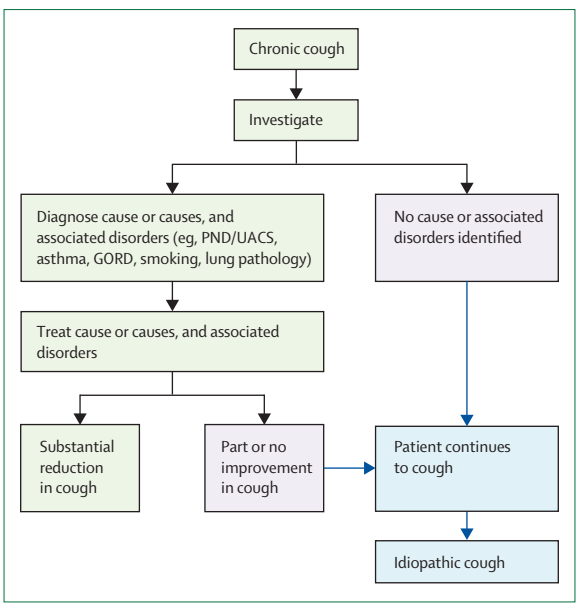

Figure 1: **Diagnostic approach to chronic cough**
PND/UACS=post-nasal drip/upper-airway cough syndrome. GORD=gastro-oesophageal reflux disease.

Mechanisms of cough hypersensitivity

Several features of the cough neural circuitry probably contribute to the development of afferent-nerve-dependent cough in disease (figure 2). First, afferent nerves are highly susceptible to sensitisation by various neuroactive molecules that change the activation characteristics of cough afferents and allow appropriate afferent encoding in response to irritant stimuli. These molecules can also change in terms of their constituents and concentrations, which perhaps underlies the manifestation of vagal neuropathies seen clinically. For example, nerve growth factor (NGF) released in the airways after antigen exposure or viral inflammation induces neuropeptide production by mechanosensitive neurons that do not normally express such molecules.[41–43] Furthermore, sensitisation might be associated with altered expression of neuronal ion channels and other receptor molecules, including TRPV1, which has an important role in the regulation of afferent nerve excitability to various chemical stimuli.[44,45] Such changes in spinal afferent neurons are known to induce spontaneous primary afferent firing (ie, independent of a peripheral stimulus),[46,47] although whether this occurs in cough fibres is unknown.

In addition to altered afferent physiology, cough hypersensitivity can manifest when normal afferent signals are amplified by central events (figure 2). Different subsets of afferent neurons functionally interact at the brainstem.[24,48,49] Simultaneous subthreshold inputs from

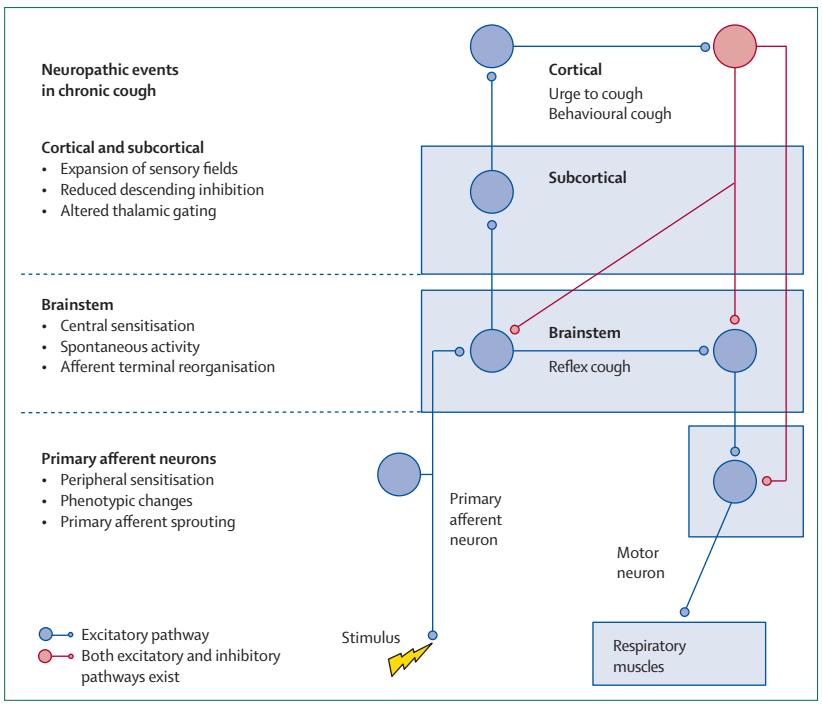

Figure 2: **Schematic organisation of brainstem reflexes and higher-order brain pathways involved in the sensorimotor control of coughing**
Neuropathic events could lead to cough hypersensitivity in disease.

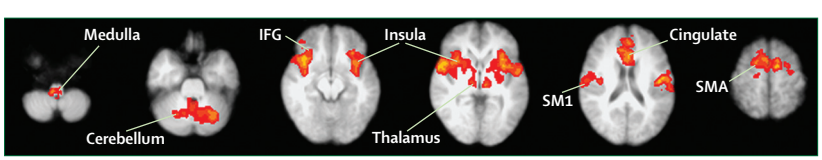

Figure 3: **Brain circuitry in coughing**
Functional magnetic resonance imaging shows capsaicin-activating responses in the brainstem, cerebellum, inferior frontal gyrus (IFG), insular cortex, thalamus, sensorimotor cortex (SM1), and supplementary motor area (SMA).

neuropeptide-expressing airway nociceptors and airway mechanosensors can substantially lower the cough-reflex threshold by virtue of the fact that they converge onto common second-order neurons in the brainstem.[24,49] Convergence of central inputs might also occur between oesophageal or airway nociceptors and airway afferent nerves.[13,50] This process of central synergy is analogous to central sensitisation noted in pain research[51] and could amplify the incoming signals that are received by the brainstem cough network, reducing the need for correct primary afferent encoding. Neuropeptides are well known for their ability to produce long-lasting excitatory effects on neurons that are receiving inputs from sensory afferents,[52,53] and so their release from peptidergic primary afferents is probably an important mechanism in the generation of central sensitisation of mechanosensory inputs in the brainstem.[24,49] For example, exposure to cigarette smoke in primates leads to increased excitability of second-order neurons in the brainstem that receive inputs from the airways, and this effect is abolished by blocking neuropeptide (substance P) neurotransmission.[54] In this respect, the induction of neuropeptide expression by airway mechanosensors after antigen or viral exposure[41–43] is an important event, since it could negate the need for convergent inputs for the establishment of central sensitisation.

Second-order medullary neurons that receive inputs from airway afferents also project to several subcortical nuclei including in the pons, thalamus, hypothalamus, midbrain, and amygdala.[33] Terminations of subcortical projections can in turn be mapped to the cingulate, insula, and the orbitofrontal and somatosensory cortices in the cerebrum.[33] In human beings, distinct neural activation patterns have been identified by use of functional brain imaging; these patterns are related to the network components that control voluntary cough, cough suppression, and the urge to cough (figure 3).[23,25,26,55] The specific responses of these network components to primary afferent activation and how they are altered in disease has not yet been described, but is of obvious importance to our understanding of chronic cough. In neuropathic pain, changes in thalamic gating of ascending afferent signals, loss of descending noxious inhibitory control, reorganisation of sensory projections onto the primary sensory cortex, and altered brain responses have all been described.[56–61] Similar central neural events are likely to underpin altered perception of airway irritation and loss of endogenous cough control mechanisms, contributing to chronic neuropathic coughing.

Can cough hypersensitivity result from neuropathology?

If cough hypersensitivity manifests from altered activity of one or more of the components of the cough neural circuitry, then is this altered activity a result of a neuropathic disorder (table)? The first step towards answering this question is to define how neuropathic cough might differ from normal physiological cough responses. The approach that has worked well for pain researchers has been to define pain as nociceptive, inflammatory, or neuropathic; this strategy differentiates the fundamental processes involved in pain derived from different sources.[62] Nociceptive pain results from an insult that supersedes the pain threshold to elicit an acute response, most akin to reflex-evoked coughing induced by inhalation of an irritant that acutely activates airway sensory nerves and drives the protective cough reflex. Inflammatory pain and neuropathic pain, however, are largely abnormal pain states that are evoked by altered neural activity associated with either tissue damage and inflammatory cell influx (inflammatory pain) or damage or disease of the peripheral sensory nervous system or its central projection pathways (neuropathic pain). Parallels could exist for cough. Thus, cough triggered by an innocuous stimulus that would ordinarily not induce this response might be akin to allodynia. Similarly, a heightened cough response to

noxious stimuli (hypertussia) could be regarded as equivalent to hyperalgesia (figure 4).

If we were to adopt this approach, we would first need to accept that vagal neuropathies could lead to cough. Admittedly, the nerve damage associated with neuropathic pain can be easy to appreciate—eg, crushing or severing of peripheral nerves associated with major trauma can lead to neuropathic pain. But pain can manifest as a result of other, less obvious, neuropathies, including viral infection, metabolic diseases (eg, diabetes), and other causes of neuroinflammation. Viral infection and exposure to allergic and non-allergic irritants cause local tissue inflammation and injury of the vagal nerves, or of their central pathways, which could contribute partly or wholly to the establishment of cough hypersensitivity (figure 5).

Inflammatory factors and neurogenic mechanisms

Chronic cough is often associated with airway inflammation and remodelling.[63] Damaged bronchial epithelium, basement-membrane thickening, and a chronic inflammatory infiltrate have been described in airway biopsy samples from patients with unexplained chronic cough.[64,65] In bronchial biopsy studies of chronic cough,[65] an increase in the number of mast cells together with features of airway-wall remodelling (characterised by an increase in vascular profiles, subepithelial fibrosis, and hyperplasia of goblet cells) have been reported. Other investigators[66–69] have reported increased numbers of mast cells and neutrophils in bronchoalveolar lavage fluid, with increases in various inflammatory biomarkers including histamine, prostaglandins D_2 and E_2, tumour necrosis factor α, and interleukin 8 in samples of sputum induced by inhalation of saline solutions (induced sputum). The expression of transforming growth factor β was increased in the airways of patients with chronic cough, and the increase was associated with the extent of airway fibrosis (as measured by the thickness of the subbasement membrane),[70] which could lead to activation of the cough reflex.

Chronic eosinophilic disorders such as asthma, cough-variant asthma, and eosinophilic bronchitis often present as chronic cough. Suppression of the eosinophilic inflammation improves cough, which suggests a potential pathogenic role for eosinophils. Eosinophils colocalise with sensory airway nerves,[71] and this contact is responsible for the release of mediators including eosinophil peroxidase and leukotrienes.[72] The neuroinflammatory effects of these eosinophil-derived mediators are well known and provide a mechanism whereby cough reflex hypersensitivity could be maintained during airway inflammation.[73] Almost 25 years have passed since inhalation of inflammatory mediators such as bradykinin and prostaglandin E_2 by healthy volunteers was shown to upregulate the capsaicin cough response.[74] The precise mechanism by which this occurs has not been established, but both mediators are known to indirectly sensitise airway neuronal responses to capsaicin, presumably via activation of the TRPV1 channel by intracellular (protein kinase) pathways.[75,76] Although the number of neural profiles in the submucosa from bronchial biopsy samples of patients with chronic cough was similar to non-coughing controls, the expression of TRPV1 on these nerves was tripled.[77] Increased hydrogen cations (H^+) in exhaled-breath condensates from patients with chronic cough has been reported,[78] which in conjunction with the increase in TRPV1 channels could form the basis for the increased cough.

Evidence exists for airway neuronal activation; raised concentrations of substance P and neurokinin A have been detected in induced-sputum samples from asthmatic coughers.[79] Furthermore, concentrations of the neuropeptide calcitonin gene-related peptide (CGRP) in airway lavage samples from paediatric patients with

	Cough as a symptom	Other symptoms and clinical features	Cough-reflex sensitivity
Laryngeal (laryngeal sensory neuropathy, post-viral vagal neuropathy, irritable larynx)	Yes (common)	Frequent throat clearing, hoarseness, weak voice, stridor, paradoxical vocal-cord dysfunction, globus sensation	Increased
Hereditary sensory neuropathy	Yes (rare)	Distal muscle weakness and wasting, reflux	Increased
Vitamin B_{12} deficiency	Yes (rare)	Anaemia, myelopathy, optic neuropathy, dementia	Increased
Diabetic autonomic neuropathy	Yes (when associated with oesophageal dysmotility)	Pain, autonomic dysfunction, sensory loss	Reduced
Neurosarcoidosis of vagus nerve	Yes (rare)	Facial pain, vocal-cord palsy	Unknown
Vagal neurofibroma	Yes (rare)	Pain , swelling, hoarseness	Unknown

Table: **Local and generalised sensory neuropathies, cough, and cough-reflex sensitivity**

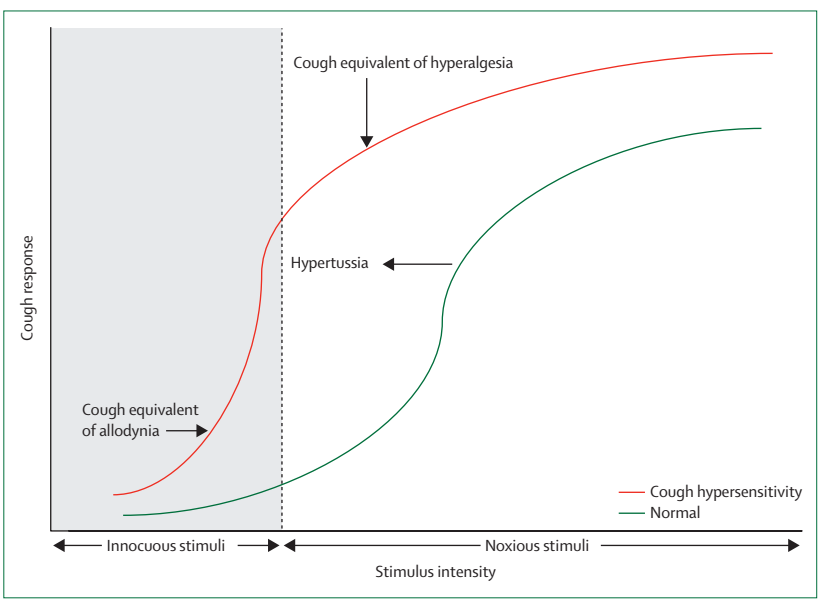

Figure 4: **Relation between stimulus intensity and cough response in cough hypersensitivity, and parallel with abnormal pain states**
Cough hypersensitivity results in cough in response to innocuous stimuli, as in allodynia.

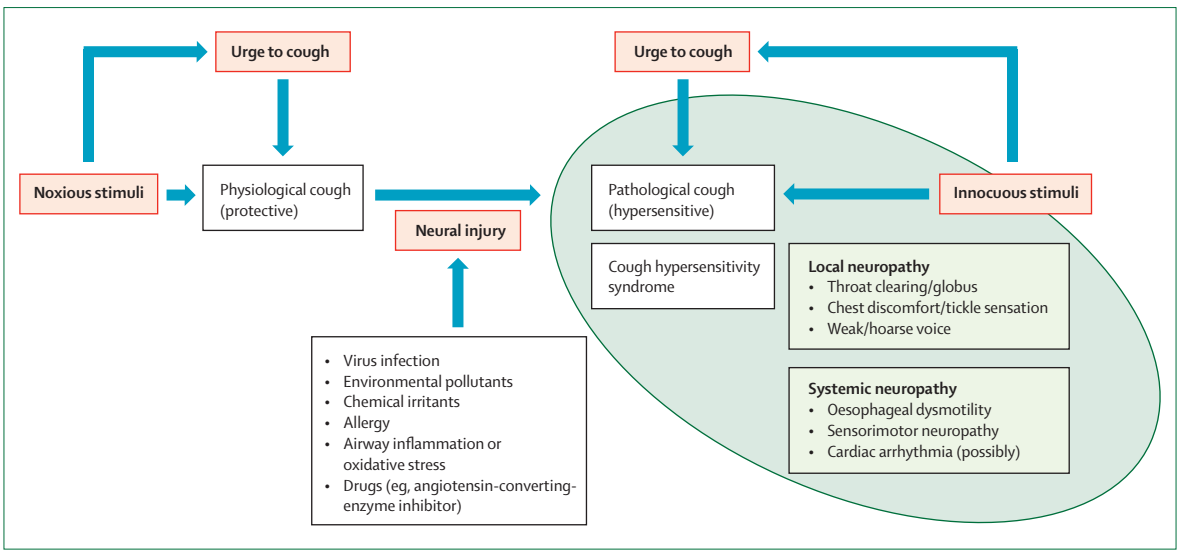

Figure 5: **Cough hypersensitivity syndrome**
The proposed effect of vagal nerve injury arises from inflammation caused by airway exposure to infective, physical, chemical, and allergic insults. The green oval emphasises the pathology (neuropathy) of the cough hypersensitivity syndrome.

chronic cough were positively associated with capsaicin-cough-reflex sensitivity.[80] CGRP expression is also increased in nerves from the airways of patients with chronic cough.[81] NGF is released from various airway cells, including the bronchial epithelium, and has neuroinflammatory effects that might be important in chronic cough. In diseases such as cryptogenic fibrosing alveolitis, in which cough is often an intractable problem, airway NGF is raised.[82] NGF can exert its action on airway sensory nerves via sensitisation of the TRPV1 receptor.[83] In primary cultures of dorsal-root-ganglion neurons from rats, NGF potentiates basal and capsaicin-induced expression of substance P and TRPV1, which suggests a mechanism for chronic nerve sensitisation.[84] In patients with airway sensory hyperreactivity to scents and chemicals, typically manifested by bouts of coughing, increased NGF has been detected in nasal secretions compared with healthy controls.[85] However, NGF concentration was not increased in bronchoalveolar lavage fluid obtained from patients with chronic cough.[70]

Respiratory viruses and cough: a neuropathic link?

Respiratory viral infections are typically accompanied by an acute cough, which can persist for weeks or months in some patients. Experimental models of rhinovirus infection have shown cough-reflex hypersensitivity to chemical[86,87] and mechanical stimulation.[88] Virus-induced neuropathic change has been described in post-herpetic neuralgia caused by reactivation of varicella zoster virus in trigeminal sensory neurons. Because this disorder is characterised clinically by hyperalgesia (heightened response to painful stimuli) and mechanical allodynia (wherein normally innocuous stimuli are perceived as painful), it represents a suitable comparison for the proposed cough-reflex sensitisation induced by respiratory viruses. In a rodent model of chronic varicella zoster virus infection, thermal hyperalgesia and mechanical allodynia were associated with an upregulation of neural-injury proteins and phenotypic change in expression of neuropeptide Y and the Nav1.8 sodium channel. Some viruses, after exposure to the airway lumen, can invade the nervous system. For this reason, herpes simplex virus has been used to anatomically map the sensory neuronal innervation of the airways,[33] which has shown the intimate relation between nerves and other structural and inflammatory cells in the airways (figure 6). Consistent with this finding, after intranasal inoculation of rodents with influenza virus, viral replication was evident in respiratory-tract epithelium after 24 h and viral antigen was consistently recovered from trigeminal and vagal ganglia and from the solitary nucleus, but with no virus detected in blood.[89,90] Human metapneumovirus, a common cause of bronchiolitis in infants (which clinically manifests as bouts of cough, wheeze, and tachypnea), has also been shown to replicate in mouse respiratory epithelium before migrating to the neuronal processes in which it persists.[91]

Evidence from antitussive therapies

The success of drugs used to treat chronic pain, such as amitriptyline and gabapentin, as antitussives also lends support to the notion of chronic cough as a neuropathic disorder. In 12 patients treated with amitriptyline, 11 had prompt, substantial reduction of their cough.[92] In a prospective, randomised, controlled, open-label trial to compare the effectiveness of amitriptyline with codeine plus guaifenesin for chronic cough with suspected post-viral vagal neuropathy, most patients in the amitriptyline group achieved a complete response, whereas none of

the patients in the codeine plus guaifenesin group had a complete response.[93] Gabapentin effectively reduced cough in patients with chronic cough in a randomised, double-blind trial, which suggests that a central reflex sensitisation occurs in refractory chronic cough.[94] Gabapentin was also beneficial in patients with chronic cough who had laryngeal sensory neuropathy.[95]

Both amitriptyline and gabapentin have central antinociceptive actions. For example, relief from rectal pain with amitriptyline is associated with a reduction in pain-related responses in the anterior cingulate cortex in people with irritable bowel syndrome,[96] although the central site of action can differ dependent on the nature of the pain.[97] Similarly, gabapentin reduces pain via modulation of GABAergic neurotransmission or voltage-gated ion channels in the spinal cord, midbrain, thalamus, and sensory and insula cortices in the brain.[98–100] Although gabapentin effectively reduced cough in patients with chronic cough,[94] it had no effect on capsaicin sensitivity, which argues against a suppressive effect on cough reflex pathways. This finding is consistent with pain studies in which these compounds specifically reduce neuropathic pain, rather than having any measurable effect on acute pain.[101,102] Since cortical responses to airway irritation share remarkable similarity with those associated with painful stimuli,[103] amitriptyline and gabapentin might reduce cough and pain via similar mechanisms at brainstem and supramedullary sites. However, amitriptyline and gabapentin can also have actions outside of the CNS, mainly by blocking the activation of peripheral afferent terminals.[98,104–106]

Case reports that document successful treatment of chronic cough with botulinum toxin injected into the thyroarytenoid muscles also suggest that chronic cough could be a neuropathic disorder. However, only four of 438 patients with laryngeal spasms and chronic cough who received injections of botulinum toxin type A into the thyroarytenoid muscle reported substantial cough relief.[107] Similarly, injection of botulinum toxin A in the vocal fold successfully reduced habit cough in three children.[108] Botulinum toxin is well known for its action at neuromuscular junctions, where it produces muscle paralysis by blocking release of presynaptic neurotransmitters. Conceivably, a reduction in laryngeal spasm could indirectly reduce laryngeal afferent activity by relieving mechanical activation of sensitised afferents. However, studies in animals have shown that botulinum toxins A and E can directly reduce the release of neurotransmitters from sensory nerve terminals, inhibit sensory nerve activation, and change the chemical coding of sensory neurons that supply the viscera.[109–112] Thus, the antitussive actions of botulinum toxin could also be related to a direct action on laryngeal sensory nerves.

What is the missing link to neuropathic cough?

The proposition that the hypersensitivity syndrome that encompasses most chronic cough is a neuropathic disorder is well supported by empirical evidence, and we have compared cough hypersensitivity with pain hypersensitivity to provide evidence for cough-pathway neuropathy. Indeed, the physiological and pathophysiological similarities between cough and pain are easily recognised,[113,114] and the evidence presented supports our assertions of a mechanistically comparable neuropathy. This similarity is most evident in the primary afferent nerves, for which both the clinical symptoms in people and work in animals are consistent with the hypothesis that peripheral sensory neuropathy can lead to altered cough sensitivity. The encouraging outcomes of clinical trials[93,94] that used centrally acting therapies add further weight to this idea. Nevertheless, the arguments that we have raised also emphasise serious gaps in research that need to be filled before cough hypersensitivity can be regarded as a neuropathology. For example, there are no direct reports of an association between chronic cough and central (brainstem) inflammation, as is the case with neuropathic pain, in which spinal microglia and other support cells are activated and a host of central inflammatory molecules act to amplify incoming primary afferent signals.[62] Similarly, changes in sensory and motor pathways above the brainstem have not yet been studied. Thus, evidence for an increased urge to cough in the absence of peripheral afferent activation would add credence to the argument in favour of neuropathic cough.

Additionally, determining whether the antitussive effects of amitriptyline and gabapentin are indeed due

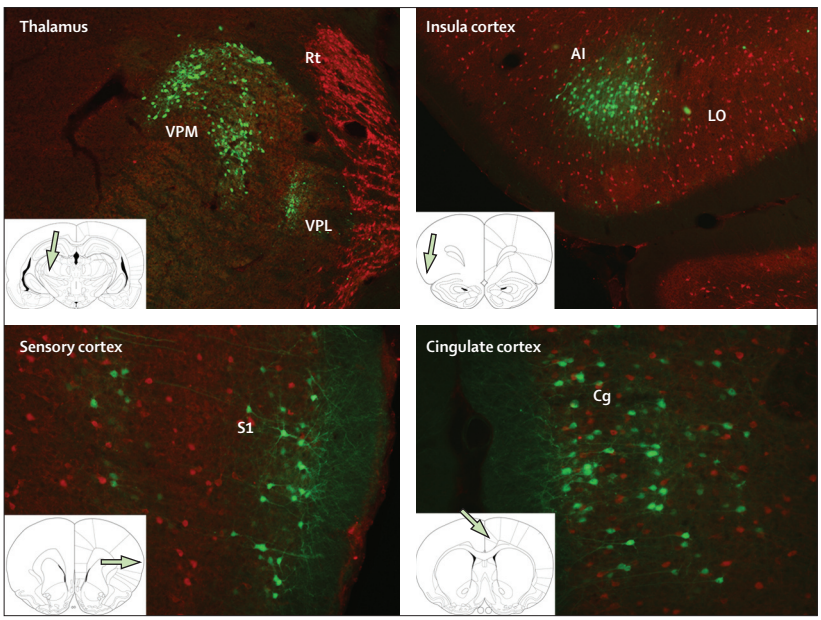

Figure 6: **Herpes simplex in the brain**
Herpes simplex virus (green) in the rodent brain after infection of the airways. Viral neurotrophism could be a mechanism that underlies neuropathic cough hypersensitivity. VPM=ventral posteromedial nucleus. VPL=ventral posterolateral nucleus. Rt=reticular thalamus. AI=anterior insular cortex. LO=lateral orbital cortex. S1=primary sensory cortex. Cg=cingulate cortex. Arrows point to the magnified area of the brain.

Search strategy and selection criteria

We searched PubMed for peer-reviewed research published in English between Jan 1, 1980, and Jan 31, 2013, using the search term "cough" in combination with "neuropathic" and "hypersensitivity". We also drew on accumulated publications gathered through our involvement in cough research and treatment during the past 20 years.

to actions at a central site (eg, by use of functional brain imaging) would add further support to our argument. In studies of chronic pain, the primary outcome most often assessed is the sensory experience of the noxious event (ie, pain perception) rather than the motor consequences (eg, the withdrawal reflex). By contrast, in studies of chronic cough, the motor consequences of airway irritation (eg, cough frequency) are assessed more often than the sensory experience (ie, the urge to cough). This difference emphasises a substantial distinction between research into chronic pain and chronic cough, and might suggest that a change is needed in the way in which we study cough hypersensitivity if we are going to define it as a sensory neuropathy. By focusing on the sensory consequences associated with cough hypersensitivity and accepting that these altered sensory events in turn drive the resultant cough response, we might be better positioned to understand how these sensory pathways become disturbed in disease, which in turn could lead to improved antitussive therapies.

Contributors

All authors contributed equally to this Personal View, including the search of the scientific literature and the planning and writing of the report. KFC composed the final submitted version.

Conflicts of interest

KFC has received honoraria for participation in an expert panel to discuss cough therapies organised by GlaxoSmithKline in 2011. He also received educational support funds for the organisation of the Seventh International Symposium on Cough in June, 2012, from Proctor & Gamble and GlaxoSmithKline. LM and SBM declare that they have no conflicts of interest.

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